REMARKS

Applicant has carefully reviewed and considered the Office Action mailed on May 7, 2002, and the references cited therewith.

Claims 34 and 38 are amended; claim 62 is newly added. As a result, claims 34-48 and 62 are now under examination in this application. Claims 1-33 and 49-61 are withdrawn from consideration in view of the Restriction Requirement.

Support for new claim 62 and for the amendment to claim 34 can be found throughout the specification, such as at page 6, lines 6-11, and page 16, lines 5-22. No new matter has been added.

Claim 38 has been amended simply to correct a typographical error.

Claim Objection

Claim 38 was objected to because a period is missing from the sentence. Claim 38 has been amended to correct this typographical error.

Rejection of the Claims under 35 U.S.C. §112, Second Paragraph

Claims 34-48 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Regarding claim 34, the examiner has indicated that it is unclear as to how a polypeptide is to be operatively linked to a nucleic acid. Claim 34 has been amended to clarify that an enzyme or protein is operably linked to a PTD, rather than to a nucleic acid sequence encoding a PTD.

Regarding claim 36, the examiner indicated that the term "soluble" lysosomal enzyme was unclear. It is recognized in the art of cell biology that the opposite of a "soluble" lysosomal enzyme is a "membrane-bound" lysosomal enzyme. For example, the lysosomal protein LAMP I is a membrane bound lysosomal protein with a portion of its structure within the lysosome, a

portion projecting into the cytosol, and a portion embedded within the membrane. These proteins, by virtue of the fact that they are membrane bound, cannot be secreted. In contrast, soluble lysosomal proteins can be secreted into the extracellular environment. Thus, the term "soluble" in the present claims is being used to indicate that these polypeptides are not membrane-bound.

Applicant requests that these rejections under 35 U.S.C. § 112, second paragraph be withdrawn.

§103 Rejection of the Claims

Claims 34-35, 37-38 and 47-48 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Schwarze *et al.* (*Science* 285:1569-1572 (1999 Sept 3)) in view of Ghodsi *et al.* (*Exp. Neuro.* 160:109-116, (1999) or *Hum. Gene Therapy* 9:2331-2340 (1998 Nov 1)).

The currently pending claims recite a polypeptide comprising a lysosomal enzyme, a naturally secreted protein, a nuclear protein, or a cytoplasmic protein operably linked to a PTD, wherein the polypeptide is expressed from an expression vector located *in situ* in a cell of a patient, and wherein the polypeptide is biologically active. Insofar as this rejection is applied to the pending claims, it is hereby traversed.

Applicant asserts that the Examiner has not established a *prima facie* case of obviousness. In order to establish a *prima facie* cases of obviousness, three factors must be met. First, the references themselves must teach or suggest all the limitations of the claims. Second, there must be a reasonable expectation of success at the time the invention was made. Third, the prior art must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference, or to combine references. Applicant respectfully asserts that the Examiner has not met these three requirements for the pending claims.

Schwarze *et al.* discuss generating full-length fusion proteins that contain an 11-amino acid PTD from HIV TAT. These proteins were generated in plasmids, and transformed into bacteria. Schwarze *et al.* at page 1572, note 11. The proteins were then purified under denaturing conditions. Schwarze *et al.*, paragraph bridging page 1569-1570. They injected mice

intraperitoneally with the fusion peptide and monitored the uptake of the peptide in brain tissue and skeletal muscle intraperitoneally. Schwarze *et al.* at page 1570.

The pending claims are distinguishable over Schwarze *et al.* in several respects. First, the protein recited by the pending claims is not isolated from bacteria; it is expressed from an expression vector located *in situ* in a cell of a patient. Second, the protein recited by the pending claims is not denatured, as was done in Schwarze *et al.* Third, the protein recited by the pending claims is not injected into the recipient animal. The protein of the present invention is expressed *in situ*. Thus, Schwarze *et al.* taken alone does not teach all the limitations of the present invention.

Ghodsi *et al.* (1998) teach intraparenchymal injection of Adβgluc, which resulted in transduction of cells in the vicinity of the injection. This also resulted in secretion and diffusion of the enzyme. Ghodsi *et al.* (1998) at p. 2338, 1st col. Ghodsi *et al.* (1999) tested the hypothesis that mannitol-induced hyperosmolality would increase the distribution of β-glucuronidase in brain following gene transfer to ependymal cells. Ghodsi *et al.* (1999) at page 110. They used an adenovirus carrying either the β-glucuronidase expression construct or a nuclear-targeted *E. coli* β-galactosidase report construct. Ghodsi *et al.* (1999) at page 111. These references do not teach or suggest a protein operably linked to a PTD, as recited by the pending claims. Thus, the Ghodsi *et al.* references do not teach all the limitations of the present invention.

Schwarze *et al.* in combination with the Ghodsi *et al.* references do not meet all three requirements for establishing a *prima facie* case of obviousness recited above. Applicant asserts that there was not a reasonable expectation of success at the time the invention was made that the invention would work. Further, Applicant asserts that the prior art does not contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference, or to combine references.

The Federal Circuit in *In re Sang Su Lee*, 61 U.S.P.Q.2d 1430-1436, 1433 (Fed. Cir. 2002) has recently stated the following:

> The factual inquiry whether to combine references must be thorough and searching. *Id.* It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with. *See, e.g., Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1124-25, 56 U.S.P.Q.2d 1456, 1459 (Fed. Cir. 2000) ("a showing of a suggestion, teaching, or motivation to combine the prior art references is an 'essential component of an obviousness holding'") (*quoting C.R. Bard, Inc., v. M3 Systems, Inc.*, 157 F.3d 1340, 1352, 48 U.S.P.Q.2d 1225, 1232 (Fed. Cir. 1998)); *In re Dembiczak*, 175 F.3d 994, 999, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999) ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."); *In re Dance*, 160 F.3d 1339, 1343, 48 U.S.P.Q.2d 1635, 1637 (Fed. Cir. 1998) (there must be some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant); *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir. 1988) ("'teachings of references can be combined only if there is some suggestion or incentive to do so.'") (emphasis in original) (*quoting ACS Hosp. Sys., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984)).

It is respectfully submitted that the Examiner is employing hindsight to arrive at Applicant's invention in the absence of any suggestion in the cited art to take Applicant's approach. The Examiner is reminded that it is impermissible to use Applicant's specification as a template to arrive at the conclusion that the claimed invention is obvious. *In re Fritsch*, 23 U.S.P.Q.2d 1780, 1782 (Fed. Cir. 1992). To render an invention obvious, the combination of the cited art must teach or suggest the claimed invention and provide a reasonable expectation of success in preparing the claimed invention. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991); *In re O'Farrell*, 853 F.2d 894, 7 U.S.P.Q.2d 1673 (Fed. Cir. 1988).

The cited art does not provide a suggestion or motivation to combine Schwarze *et al.* with Ghodsi *et al.* As discussed above, Schwarze *et al.* disclose preparing a PTD linked protein in bacteria, denaturing it, and injecting the protein into a target tissue of an animal. Schwarze *et al.* do not teach or suggest the possibility of generating a vector containing the nucleic acid encoding the PTD linked protein, and injecting the vector into an animal so as to obtain proteins generated *in situ.* The Ghodsi *et al.* references discuss preparing a vector containing nucleic acid sequence

that encodes a target protein. The Ghodsi *et al.* references do not suggest the use of a PTD sequence. Applicant asserts that the motivation to generate a vector containing the nucleic acid encoding the PTD linked protein, and then to inject the vector into an animal so as to obtain proteins generated *in situ* only arose from Applicant's own specification.

Even if the Examiner argues that Schwarze *et al.* in combination Ghodsi *et al.* provided a motivation to combine the references, Applicant respectfully asserts that there would not have been a reasonable expectation of success at the time the application was filed that the claimed polypeptide (a lysosomal enzyme, a naturally secreted protein, a nuclear protein, or a cytoplasmic protein operably linked to a PTD) could effectively be expressed from an expression vector located *in situ* in a cell of a patient. Schwarze *et al.* did not generate PTD-linked protein *in situ*; it was harvested from bacteria, denatured, and then injected into tissue. Ghodsi *et al.* generated protein *in situ*, but it was not PTD-linked protein. It was not known prior to the experiments by the present inventors that a PTD-linked protein generated *in situ* in a cell (*i.e.*, inherently not denatured) would be expressed. In fact, the art taught away from a non-denatured PTD-linked protein being active *in situ*. Schwarze et al. in the paragraph bridging page 1571 to 1572 states:

> A previous attempt to transduce β-Gal chemically cross-linked to the TAT PTD into mice resulted in sporadic and weak β-Gal activity in a limited number of tissues, with no activity detected in the kidney or brain. Th increased transduction potential reported here likely reflects the inframe fusion and purification strategy. (Emphasis added)

Thus, Schwarze *et al.* teach away from the present invention. Those skilled in the art (namely, Schwarze *et al.*) taught that PTD-linked β-Gal had no activity in the brain, which is why they denatured the PTD-linked protein before administering it to the animal. Thus, one of skill in the art would not have expected that a PTD-linked enzyme generated *in situ* in the cells of a patient would have been enzymatically active.

The Ghodsi *et al.* references do not remedy the deficiencies of Schwarze *et al.*, as Ghodsi *et al.* do not discuss PTD-linked enzymes. They would not have known until after the present inventions were carried out whether or not a PTD-linked enzyme generated *in situ* in the cells of a patient would have been enzymatically active.

Thus, even when combined, these references do not meet all three requirements for *prima facie* obviousness. Applicant requests that the rejection of the pending claims under 35 U.S.C. § 103(a) be withdrawn.

Rejection of the Claims under 35 U.S.C. §112, First Paragraph

Claims 34-48 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the examiner states that a protein linked to a nucleic acid is not enabled by the specification. As discussed above, the present claims have been amended to recite a protein (*i.e.,* a lysosomal enzyme, a naturally secreted protein, a nuclear protein, or a cytoplasmic protein) is operably linked to a PTD. Therefore, this rejection is rendered moot.

The examiner states that claims 34-37, 39-46 are rejected under 35 U.S.C. § 112, first paragraph because the specification, while being enabling for a polypeptide comprising β-glucuronidase, does not reasonably provide enablement for other enzymes.

Applicant asserts that the present claims as amended are fully enabled by the specification. Applicant performed proof-of-principle experiments (Example 3; and page 14, line 9 through page 17, line 2) that a protein linked to a PTD could be expressed from an expression vector *in situ* in a cell of an animal and be enzymatically active (*i.e.*, biologically active). Once the present inventors successfully tested these PTD polypeptides *in situ*, it would be within the skill of an ordinary artisan to generated the other proteins encompassed by the present claims. For instance, Schwarze *et al.* at page 1570 found that they could transduce over 50 proteins ranging in size from 15 to 120 kD into a wide variety of human and murine cell types *in vitro*. It should be remembered, though, that Schwarze *et al.* only tested *in vitro*, and not *in situ*, and that Schwarze et al.'s experiments resulted in inactive proteins. Some experimentation might be needed in order to test all the possible new proteins that would be covered by Applicant's application, but the amount of experimentation would not be undue in view of teaching of the present specification.

Further, Applicant has performed experiments testing the soluble lysosomal protein TPP-I, and found that, like β-glucuronidase, TPP-I also remains enzymatically active when modified to contain a PTD motif. Declaration of Dr. Davidson (9 September 2002), ¶ 3, submitted herewith. Thus, the specification is enabled for other enzymes.

Applicant requests that these rejections under 35 U.S.C. § 112, first paragraph, be withdrawn.

Conclusion

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (612-373-6961) to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner of Patents, Washington, D.C. 20231, on this 9th day of September 2002

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Name

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Signature